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TITLE: Detection of Prostate Cancer Utilizing Monoclonal Antibody J591 and Intraoperative Beta and Gamma Cameras

PRINCIPAL INVESTIGATOR: Steven Larson, M.D.
Farhad Daghighian, Ph.D.

CONTRACTING ORGANIZATION: Sloan-Kettering Institute for Cancer Research
New York, New York 10021

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Steven Larson, M.D.
Farhad Daghighian, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Sloan-Kettering Institute for Cancer Research
New York, New York 10021

E*Mail: larsons@mskcc.org

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14. ABSTRACT
The hypothesis of this project is that these novel cameras, applied during surgery on prostate cancer patients after being injected by radiolabeled antibody J591, would detect small pieces of cancerous tissue that would otherwise remain undetected. According to our project, a group of prostate cancer patients who are scheduled for surgery, will be injected with radiolabeled J591 mAb. Then our cameras will be used during surgery to locate any involved lymph node, or tissues at the margins of the resected prostate that may be infiltrated by cancer. Also, we planned to use our flexible beta camera to locate the best site in transrectal biopsies using Y-90 labeled mAb. According to our plan, the first year was devoted to development of the novel instrumentation for detection of prostate tumors. This task was successfully completed. The next eighteen months was devoted to testing and characterizing the devices in laboratory and improving them as needed. This task was also successfully completed.

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FOREWORD

We have produced a monoclonal antibody that specifically binds to a prostate specific membrane antigen. This compound, called J591, has been labeled with radioactive isotopes In-111 and Y-90.

We have developed three novel cameras that are capable of efficiently detecting a wide variety of radioisotopes that emit gamma or beta rays. They are small and can enter the body during open surgery or endoscopic procedures to provide better images in a shorter time, and more importantly, in real time, while the surgery is proceeding. These include: a hand held beta camera, a flexible beta camera, and a hand-held gamma camera.

The hypothesis of this project is that these novel cameras, applied during surgery on prostate cancer patients after being injected by radiolabeled antibody J591, would detect small pieces of cancerous tissue that would otherwise remain undetected. According to our project, a group of prostate cancer patients who are scheduled for surgery, will be injected with radiolabeled J591 mAb. Then our cameras will be used during surgery to locate any involved lymph node, or tissues at the margins of the resected prostate that may be infiltrated by cancer. Also, we planned to use our flexible beta camera to locate the best site in transrectal biopsies using Y-90 labeled mAb.

According to our plan, the first year was devoted to development of the novel instrumentation for detection of prostate tumors. This task was successfully completed. The next eighteen months was devoted to testing and characterizing the devices in laboratory and improving them as needed. This task was also successfully completed.

The clinical trials of the these instruments were delayed due to humanizing the antibody and delays in obtaining IRB approval.

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Task 1) scintillation detector for the gamma camera [Status : Complete]

During the past year a novel scintillator, called LSO, was introduced to market by the CTI Corp. We conducted a design research for use of LSO instead of NaI(Tl) scintillator. In order to determine imaging performance, light collection response studies were conducted by simulating the response to point light sources whose origin was varied throughout the crystal radially. Optical photon tracking simulations were performed for 60 cm diameter NaI(Tl) and LSO disks coupled to a PMT. For the NaI(Tl) a 13 mm thick disk was studied 13.0 mm for 174keV Photons of In-111. For the LSO disk the corresponding thickness was 5.0 mm. The goal of these simulations was to determine the light distribution properties for these crystals. Simulations were performed with a modified version of DETECT [1]. The top surface is painted with a white diffuse Lambertian reflector that preferentially reflects light toward the photo cathode, and all other surfaces are polished for optimal light transmission. The z coordinate or depth of these point sources of light was fixed at the average depth of interaction in that crystal for a given gamma ray energy. The probability that a gamma ray interacts in a crystal decreases exponentially with depth. The mean interaction depth was then calculated using this exponential distribution. For a NaI(Tl) crystal of 13 mm thickness, this average depth is 4.8 mm for 174 keV gamma rays emitted by In-111. The mean depth was taken as 2.0 mm in the 5.0 mm LSO disk thickness. These point sources of light simulate the effect of a single gamma ray photoabsorption.

Results: Figure 1 shows images of the light photon intensity distribution that impinges on the photocathode for a point flash of light consisting of 6600 light photons created in the 13 mm thick NaI(Tl) disk (left) and 4600 photons [2] in the 5 mm LSO disk (right).

Figure 1. The photon distribution in 13 mm thick, NaI(Tl) (left); and 5 mm thick LSO (right)

Studying the fraction of photon transported to the PMT photocathode in NaI(Tl) and LSO, demonstrated that even though NaI(Tl) has over 40% more light yield, its lower gamma ray stopping power dictates that it must be over a factor of two thicker than an LSO disk of equivalent stopping power, resulting in lower light collection efficiency for the NaI(Tl) for these particular configurations.

The profiles of light distribution at various locations were fitted to Lorentzian distribution. Figure 4 shows plots of the peak position (left) and width (right) of the distributions for NaI(Tl) (10 and 13 mm thick) and LSO (3.5 and 5 mm thick) for the 140 and 174 keV energy and the seven source positions.

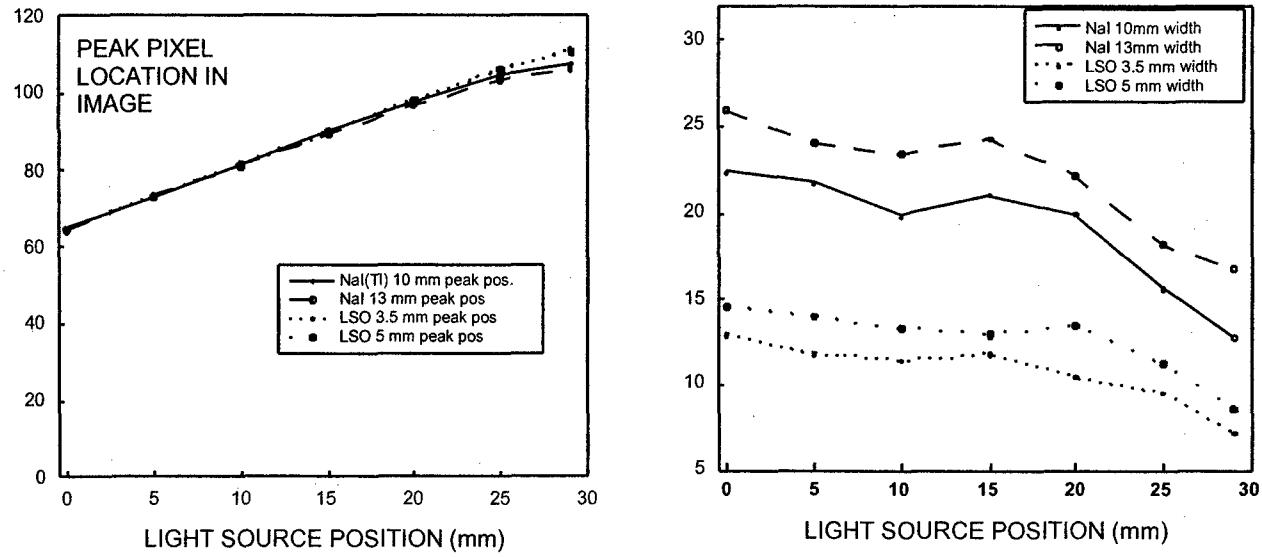

Figure 2. Left, peak locations and right, width of the photon intensity profiles for 140 and 174 keV interactions in the NaI(Tl) and LSO disks.

The point of maximum intensity for the light distributions (related to event position) in NaI(Tl) and LSO follow roughly the same, nearly linear curve for all the radial source distributions. Toward the edge of the detector LSO curve is more linear. The major advantage of LSO is demonstrated in its narrower light spread function (Fig. 2, right). This advantage translates into better spatial resolution compared to that for the NaI(Tl).

Conclusion: We have simulated light distribution properties in NaI(Tl) and LSO disks optimized for the detection of 174 keV gamma rays emitted by In-111. The lower gamma ray stopping power of NaI(Tl) dictates that it must be over a factor of two thicker than an LSO disk of equivalent stopping power. Thus, even though NaI(Tl) has over 40% more intrinsic light yield than LSO, the latter has more desirable properties in terms of higher light transmission (Figure 1) and narrower light spread function (Figure 2, right). Since there is a direct correspondence between scintillation imaging signal-to-noise ratio and light collection efficiency and between spatial resolution and light spread width, **we conclude that LSO is the scintillator of choice for this particular application.**

Experimental Evaluation of LSO for camera **[Status: Complete]**

LSO crystals were purchased from CTI Corp. and were cut and polished to two discs of 60 mm diameter and 3.5 and 5 mm thick. One potential problem in using LSO was the existence of a natural radioisotope of lutetium with long half-life radioactive decay. We measured the intrinsic count rate of a 60 mm diameter, 5 mm thick crystal to be 300 cps

in the energy window of 150-200 keV. Considering that this background noise is evenly distributed over the field of view, and is low compared to the count rates from tumors (by a factor of at least 100), therefore this would not cause any problem in the clinical detection of the tumors.

Task 2) Trans-Rectal Beta Camera: [Status: Completed]

This instrument is designed to image the distribution of Y-90 labeled antibody against prostate cancer, through the rectal tissue. Several optical fiber bundles were tested to identify the best light transmission. A bundle of fiber optics was identified with a 8 mm diameter, containing 15 fibers per mm. It was bent to a 30 degrees, 15 mm from its tip. The overall length of this imaging-grade fiber bundle is 150 mm. A 0.5 mm thick plastic scintillator was glued at the bent tip of the fiber. Aluminized Mylar (0.05 mm thick) was used to stop the entry of visible light. This imaging-grade fiber bundle transmitted 20% of the scintillation light emissions of the plastic scintillator (420 nm). This fiber bundle was mounted on a novel type of PS-PMT with an area of 1x1" (Hamamatsu R7600 C-12).

The sensitivity of this camera was determined to be 2100 cps/microCi, using a point source of F-18 in contact with the face of the camera

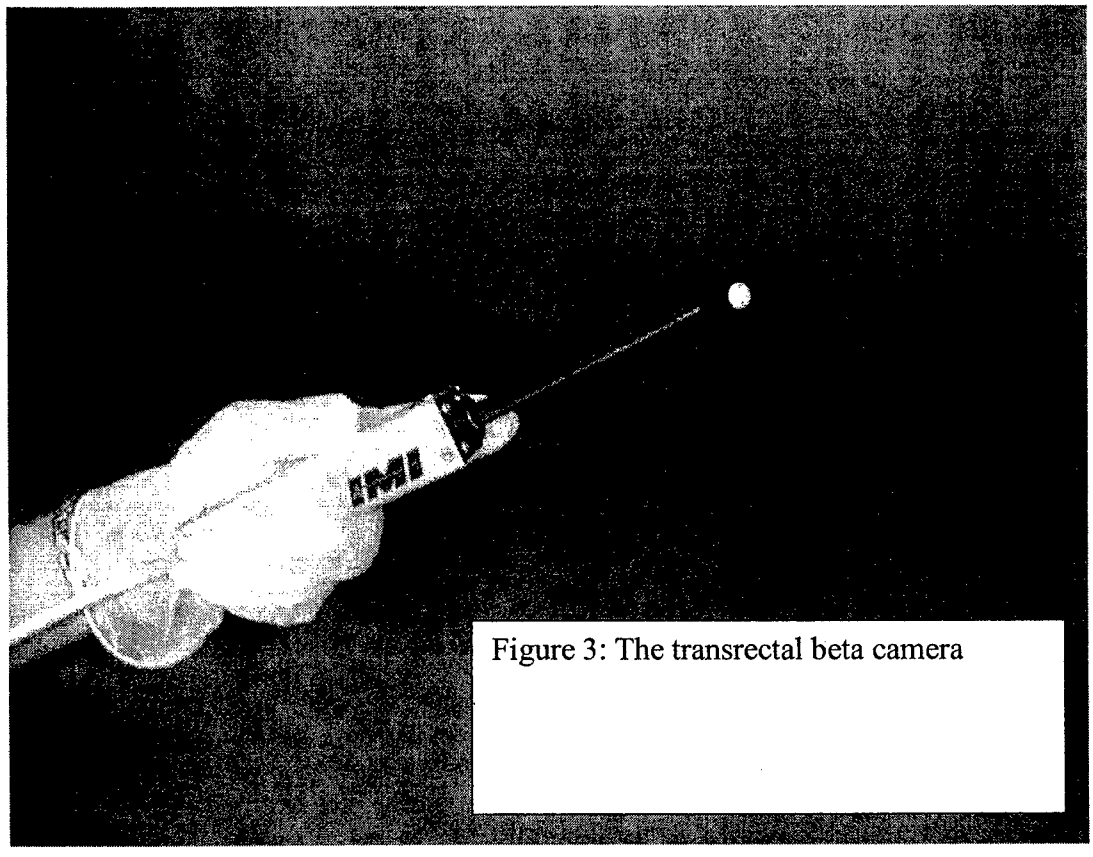

Figure 3: The transrectal beta camera

Task 3) Electronic Circuits for the Cameras:

The cameras utilize Hamamatsu's position sensitive PhotoMultiplier Tube (PS- PMT). The PMT's face is bonded to a plastic scintillator for the beta cameras, and LSO scintillator for gamma camera . The following electronic circuits were designed and built.

Analog Section: **[Status: Completed]**

1) The PMT front end electronics :
   a) The pre-amplifier circuits required for signal amplification
   b) The high voltage divider.
   c) Resistor chains for decoding of the position, and the variable resistors for adjustment of uniformity and enlargement of the field of view.

These circuits were designed and built, using surface mount components for compactness, on one small board that is mounted on the back of the PSPMT. This way the gamma camera is contained in a cylindrical housing of 3.5" diameter and 3 " height.

Second-level electronics: **[Status: Completed]**

This board further amplifies the signals and integrates them. A discriminator circuit sets the upper and lower energy limits, and only those signals that fall into this window are held for digitization. These levels and the high voltage supply (mounted on this board) are adjusted by software. Once a valid signal is detected, the four identical integrate-and-hold circuits operate on the Xa, Xb, Ya, and Yb, signals respectively. This captures the position information. The pulse that is generated also acts as the digitizing pulse for A/D conversion.

Digital Electronic Circuits: **[Status: Complete]**

Each signal, Xb, Xb, Ya, Yb, is routed to its own LPTAD8FIFO board. The LPTAD8FIFO is a high speed (>1 MSample/s) 8 bit A/D converter containing up to 64K of onboard FIFO RAM. The LPTAD8FIFO board allows the unattended collection of information from the X-Y PMT with little or no processor overhead. Xb, Ya, and Yb, values are automatically digitized whenever a valid pulse is generated from the detection threshold circuitry. These values are buffered in the FIFO until the FIFO is either unloaded or full. The digitized values are transferred to the CPU of a lap-top computer.

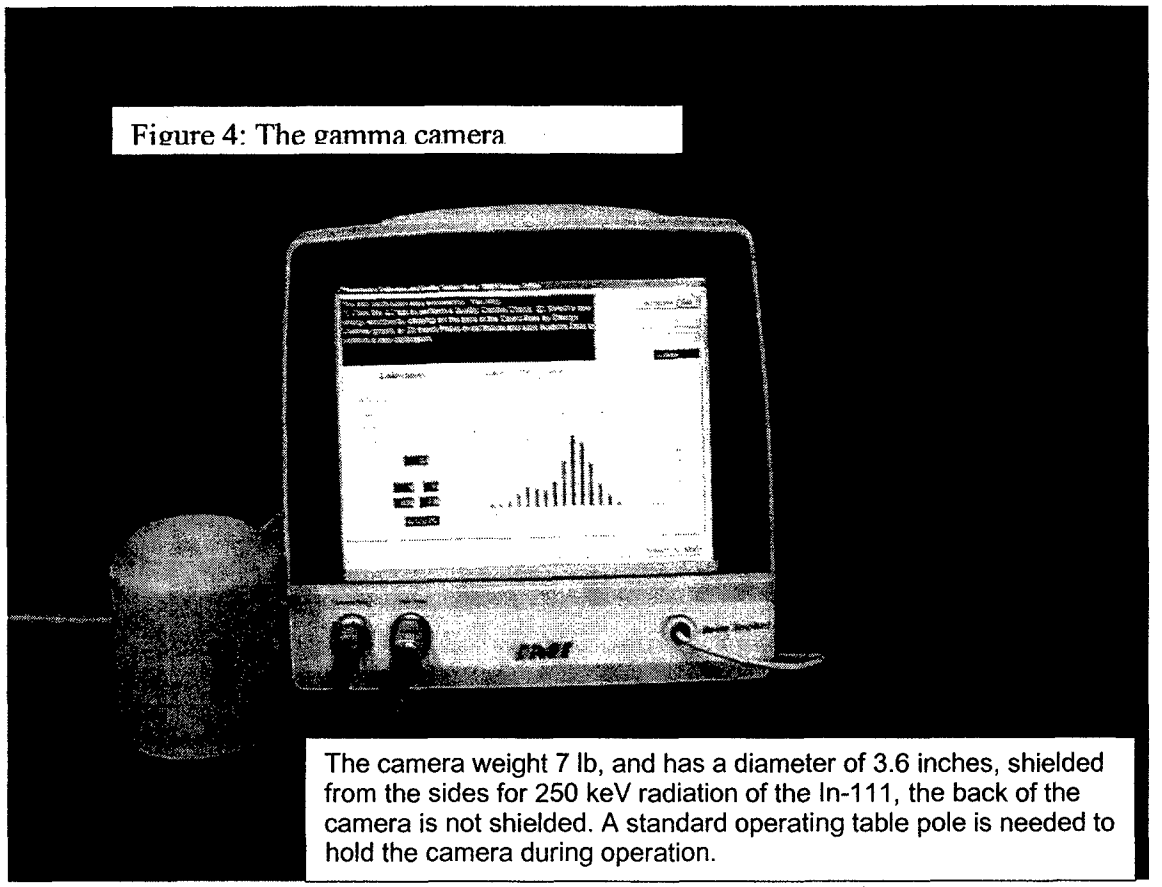

Figure 4: The gamma camera

The camera weight 7 lb, and has a diameter of 3.6 inches, shielded from the sides for 250 keV radiation of the In-111, the back of the camera is not shielded. A standard operating table pole is needed to hold the camera during operation.

Task 4) Software: **[Status: complete]**

The software was developed to transfer the digitized signals to the computer, calculate the position and the total energy of the radiation event, form the image, correct the image for uniformity, display it for the user repeatedly.

The following is a summary of the functions preformed by the software:

1) calibration / quality control software offers a menu of available calibration/quality control procedures, leads the user through the required steps, gathers data from the camera for inspection by the user, asks the user to specify or verify the continued validity of current parameters, and finally records the session.

2) setup step recalls stored hardware parameter values (determined during calibration) and sends them to the Data Acqusition section.

3) Data Acquisition. The software forms an image from the four set of numbers received from the FIFO, and correct the image for nonuniformity in gain (using a lookup table accumulated in the calibration proceedure), accumulate the images every 0.1 second and display the sum image every 2 seconds. This process continues until the operator pushes the foot pedal. Then the operator is asked to discard the data (this is the default: by pushing the foot pedal again), or entering the data regarding the region of the imaging.

4) Data Base. The file name is typed after the image is collected, together with the name of the patient and location that the image was taken.

5) Image analysis: simpele tools such as region of interest and line profile analysis are developed for analysis of the images.

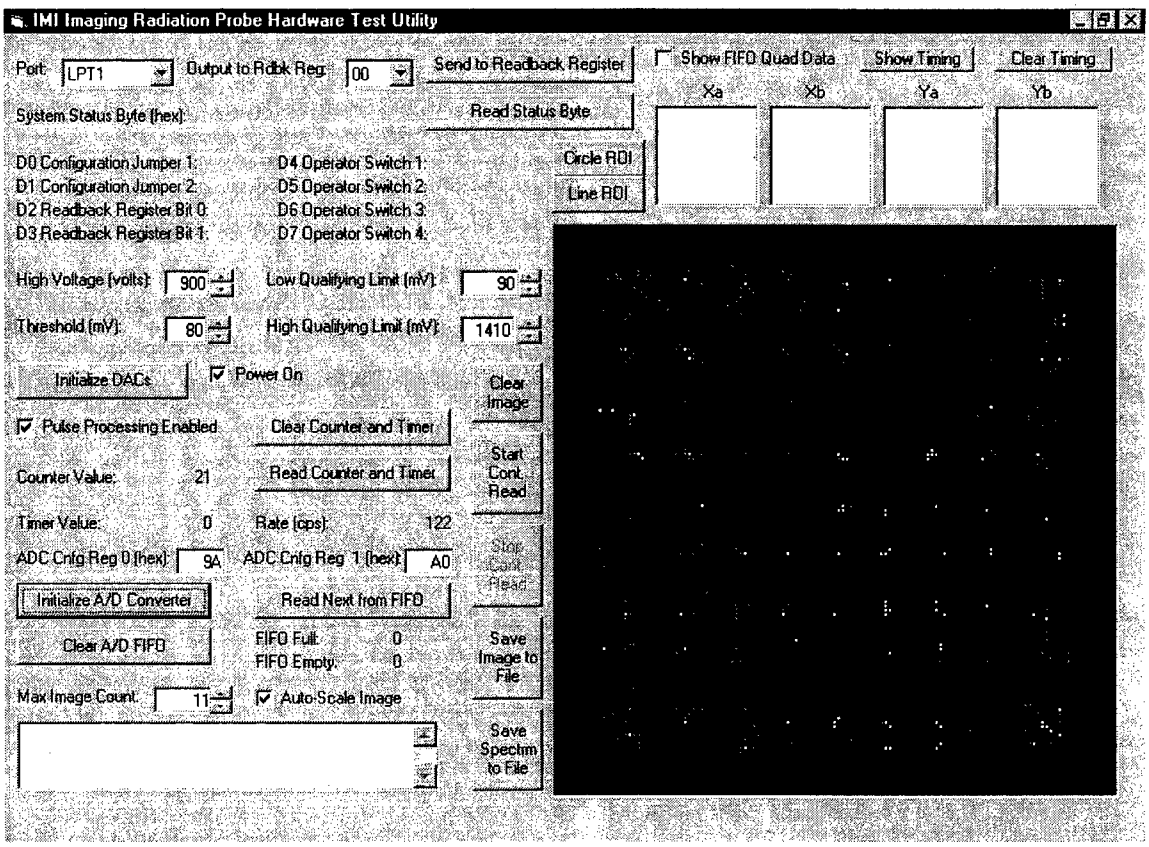

Figure 5: the main screen of the camera software. An image taken by the beta camera from a phatom of point sources of F-18 is also shown.

Task 5: Beta Camera Construction and testing (Status: Complete)

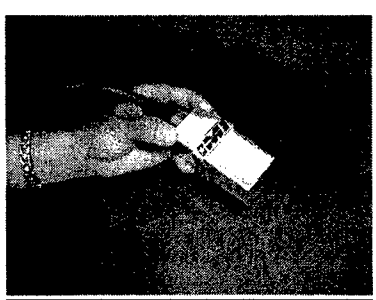

Figure 6: Beta camera, having a field of view of 22x22 mm.

This camera was built by coupling a thin sheet of plastic scintillator was coupled to a PS-PMT (Hamamatsu C-12), the face of the camera is covered by thin aluminized mylar. An image taken by this camera from a phantom of F-18 point-sources is shown in Figure 4. The sensitivity of this camera for F-18 was determined to be 3400 cps/microCi in contact.

Task 6) Results of the Gamma Camera Tests: (Status: Complete)

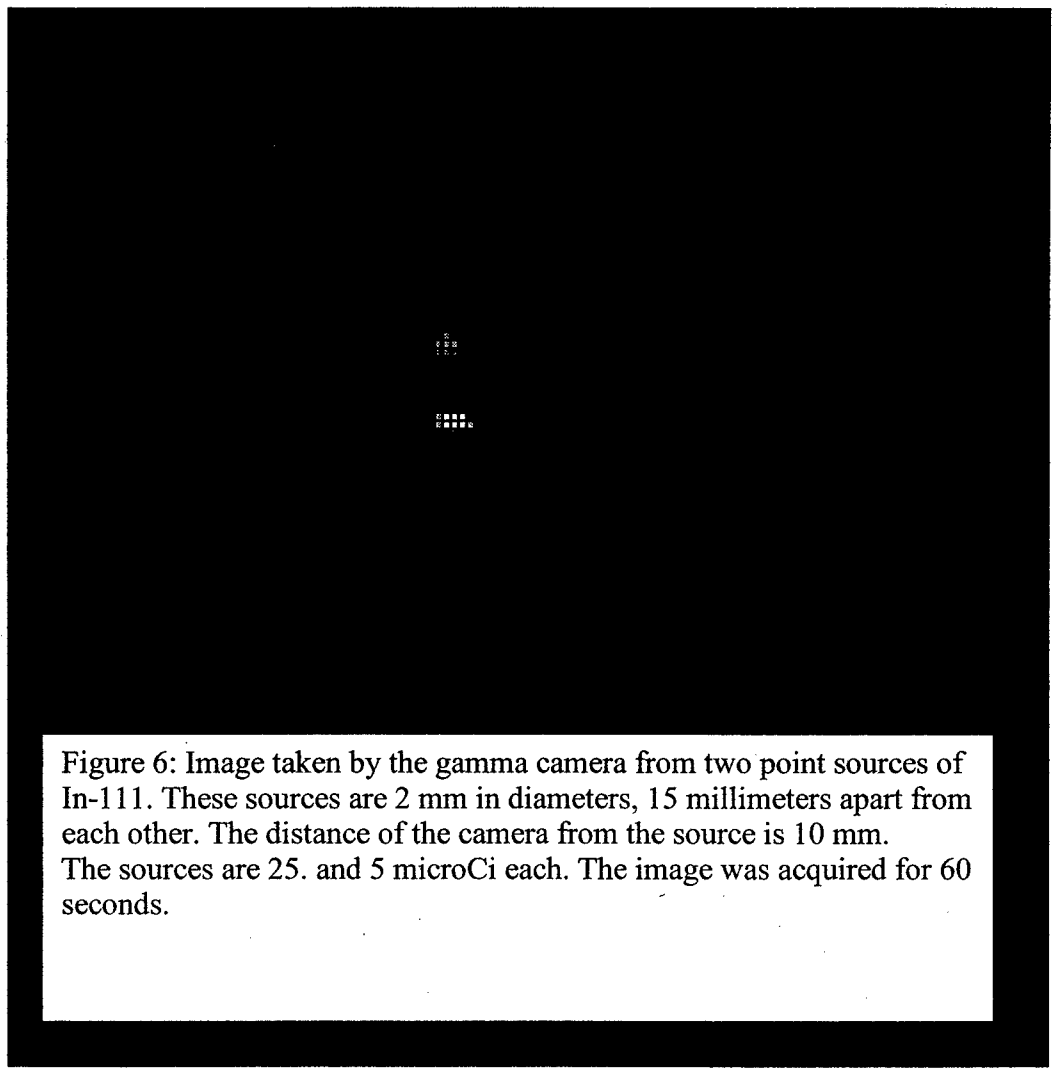

Figure 6: Image taken by the gamma camera from two point sources of In-111. These sources are 2 mm in diameters, 15 millimeters apart from each other. The distance of the camera from the source is 10 mm. The sources are 25. and 5 microCi each. The image was acquired for 60 seconds.

The followings are the characteristics of the camera for imaging In-111 .

Physical:

The camera weight 7 lb, and has a diameter of 3.6 inches. The camera is shielded from the sides for 250 keV radiation of the In-111, the back of the camera is not shielded. An standard operating table pole (those that clamp onto the rails of the operating table) should be used to hold the camera.

Performance:

The spatial resolution at 1 cm from the face of the collimator is 5.5 mm FWHM.
The sensitivity at 1 cm from the face of the collimator (in air) is 273 cps per microCi.
The field of view is 2 inches in diameter.

Note: the above sensitivity and resolution is for 174 keV emission of In-111. The software is not capable of acquiring images in two windows simultaneously.

Conclusion

The research conducted during this project resulted in an important discovery in nuclear imaging technique, namely, the superiority of LSO over NaI(Tl). This discovery changed our original design. New scintillator and collimator system was designed and built. The electronic system was also designed and built. The software for image acquisition, display, and analysis was developed. The performance of the instruments developed in this project were determined by phantom studies. More studies with animals and humans are planned in the near future.

References:

[1] G.F. Knoll, T.F. Knoll, and T.M. Henderson. Light Collection in Scintillation Detector Composites for Neutron Detection. IEEE Trans. Nucl. Sci. 35 (1988) 872-5.

[2] M. Moszynsi, M. Kapusta, M. Mayhugh, D. Wolski, S.O. Flyckt. Absolute Light Output of Scintillators. IEEE Trans. Nucl. Sci. 44(3) (1997) 1052-61.

Publications

n/a

Personnel Receiving Pay

- David Cheng
- Farhad Daghighian
- Steven Larson
- Larry Poon
- Michael Reznikov
- Pat Zanzonico

Graduate Degrees

n/a

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

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